

MAJOR REVIEW

Cutaneous Malignant Melanoma Metastatic to the Eye, Lids, and Orbit

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Abstract. The incidence of malignant cutaneous melanoma is increasing faster than any other cancer. Thus, it will become an increasingly common source of metastatic disease to the eye, lids, and orbit. Herein, we have performed a systematic review of previously published cases including patient characteristics, clinical presentation, diagnostic techniques, current treatments, and outcomes. At the time of ocular diagnosis, nearly all reported patients had a known history of cutaneous melanoma and synchronous non-ocular metastases. Several aspects help in differentiating the tumors from primary uveal melanomas such as the presence of symptoms, rapidly growing multifocal tumors, vitreous seeding, and histopathological findings. Intraocular metastases (uvea, vitreous, retina, and anterior-segment) are more common and occur in younger patients than extraocular metastases (eyelids, orbit, and extraocular muscles). Palliative radiation therapy is often used for intraocular disease. Orbital metastases from cutaneous melanoma commonly involve the extraocular muscles resulting in diplopia and exophthalmos. The mainstays of extraocular treatment are surgical resection and radiation therapy. Unfortunately, there are few good options for systemic treatment of diffusely metastatic melanoma. Therefore, patients with ocular metastasis should be managed to prevent loss of vision or loss of the eye, and to maximize their quality of life. (*Surv Ophthalmol* 53:187–202, 2008. © 2008 Elsevier Inc. All rights reserved.)

Key words. cutaneous • eye • glaucoma • malignant melanoma • metastatic • ocular • orbit • seeding • vitreous

I. Introduction

A. OVERVIEW OF THE LITERATURE

Cutaneous malignant melanoma typically spreads to ocular structures in the setting of advanced metastatic disease.⁵² However, it can also be the first sign of metastasis.^{3,15,68} As the incidence of metastatic cutaneous melanoma increases, early recognition of ocular metastasis will offer the best chance to preserve the patient's quality of life.^{3,15,68}

Several large-scale reviews have described characteristics of various cancers metastasizing to the eye, lids, and orbit. Relatively small reviews on cutaneous

malignant melanoma metastasizing to the eye or orbit have been published. They examine a body of literature that is mostly composed of anecdotal case reports, comparisons to primary choroidal melanoma, epidemiology, or small studies focused on genetics or treatment. Autopsy studies have also reported on the incidence of asymptomatic ocular melanoma metastases.²⁶ To date, we could find no encompassing reviews on metastatic cutaneous melanoma to all ocular structures.

In 2003, Zografos et al reported the largest and most recent study of 12 patients with cutaneous

melanoma metastatic to the eye and orbit.⁸⁰ Similarly, Ramaesh et al summarized literature of intraocular metastases from cutaneous melanoma (reporting a total of 68 eyes).⁵⁵ By combining prior reviews and a multitude of case reports together with our clinical experience, we present a comprehensive study of the characteristics of patients with ocular, adnexal, and orbital metastases from cutaneous melanoma. This review summarizes published patient characteristics, ocular presentations, features of metastatic disease, treatments, and patient outcomes.

We realize the potential for selection bias in this type of comprehensive report. Clearly, in such a broad array of studies and reviews, data are gathered differently with various patient populations, analyzed with different measures and objectives, and presented with a variety of purposes. However, in combining this multitude of information we descriptively, albeit not statistically, provide an overall picture of the world's experience with ocular metastatic cutaneous melanoma.

B. SYSTEMIC METASTASES FROM CUTANEOUS MELANOMA

Malignant melanoma is the ninth most common cancer and the leading cause of death from cutaneous malignancy.⁷² Although early detection and surgical cures are common, stage IV disease (distant metastases) still accounts for 5% of melanoma cases and is associated with 5-year survival rates of only 22%.⁷³

The eye is a rare site of distant metastases from cutaneous melanoma but the lung is common occurring in 18–36% of patients.²⁷ Although some studies have shown that over half of patients with metastatic cutaneous melanoma have lung metastases, most metastases first spread to the lymph nodes, skin, and subcutaneous tissues (42–57% of patients).^{2,27} Liver (14–29%), brain (12–20%), and bone (11–17%) are other common sites of metastasis.^{2,27}

C. METASTASES TO THE EYE AND ORBIT

Breast cancer, followed by lung and then unknown primary, are the most common malignancies to metastasize to the eye and orbit (accounting for over 75% of all ocular metastases).^{12,29,32} Cutaneous melanoma has been reported to be the 4th or 5th most common although it accounts for less than 5% of all metastases to the eye and orbit.^{12,29,32}

Consider the following relatively large studies of intraocular metastatic disease from systemic cancers. Castro reviewed 126 eyes with metastatic tumors finding that 49 eyes had primaries from the breast, 22 from the lung, 22 from unknown primaries, 11

from neuroblastoma, and 4 from cutaneous melanoma.¹² Freedman and Folk reported on 112 patients with metastatic disease to the eye.²⁹ Of these, breast primaries accounted for 55 patients, lung 16, unknown primaries 9, and cutaneous melanoma accounted for 5.²⁹ Therefore, cutaneous melanoma accounted for 3.2% and 4.5% of primaries metastatic to the eye.^{12,29}

In a review of metastatic tumors to the orbit, Goldberg et al found the breast to be the most common primary source (accounting for 42% of patients), followed by lung and unknown primary at 11% each.³² Prostate cancer was the primary in 8% and cutaneous melanoma in 5%.³² Other studies have suggested that cutaneous melanomas can account up to 15% of all orbital metastases.⁸⁰

Autopsy studies typically report larger numbers because they include patients with asymptomatic and end-stage metastatic cutaneous melanoma. The overall incidence of orbital and intraocular involvement has been reported from 1% up to 33% in autopsy series.^{26,55} Although up to a third of patients with diffusely metastatic cutaneous melanoma have ocular metastases, it may be related to end-stage dissemination throughout the body prior to death.⁸⁰

D. DIAGNOSIS OF METASTATIC CUTANEOUS MELANOMA

1. History and Clinical Examination

Differentiation between primary and metastatic intraocular melanoma can be difficult. A history of cutaneous melanoma and synchronous nonocular metastases is an important indicator.^{15,17,19} Metastatic cutaneous melanomas typically grow more rapidly and are more aggressive than primary uveal melanomas.^{3,7} In addition, metastatic melanomas in the uveal tract tend to be relatively flat and multifocal (Fig. 1).^{28,33} Like most choroidal metastases, these cutaneous melanoma metastases are not likely to exhibit mature vasculature or fluorescein leakage (Fig. 2). However, exudative retinal detachments can occur. Both primary and metastatic choroidal melanomas will produce a transillumination shadow (Fig. 3). A diagnosis of metastatic cutaneous melanoma must be considered when bilateral, diffuse, and multifocal ocular melanomas are seen (Fig. 1).^{17,33}

Clumps of pigmented cells in the vitreous or on the lens surface suggest metastatic cutaneous melanoma but have also been reported with primary uveal melanomas (Fig. 4).^{10,35} It has been postulated that metastatic cutaneous melanoma is less likely to produce discrete tumor masses because individual melanoma cells gain access to the vitreous

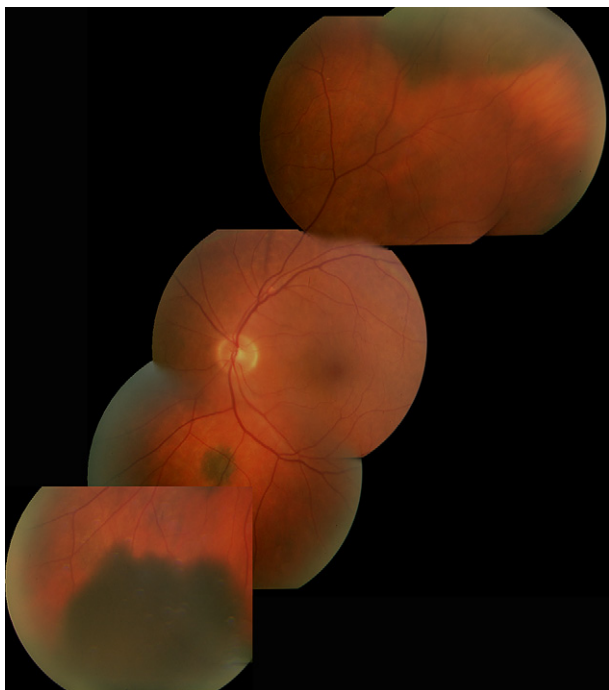


Fig. 1. Cutaneous melanoma metastatic to the eye and orbit. A composite fundus photograph reveals multifocal, relatively flat uveal metastatic melanoma of cutaneous origin.

through the pars plana and adjacent retina.¹⁰ Another possible mechanism for vitreous invasion is the budding of spherules from the optic disk pinching off into the vitreous.⁵⁴ Vitreous seeding typically occurs with concurrent retinal, ciliary body, optic disk, and iris disease, suggesting these cells are directly released from these structures.^{35,68} Though disseminated pigmentation may suggest melanoma, it has also been confused with hemosiderin or



Fig. 2. Cutaneous melanoma metastatic to the eye and orbit. *Left:* A composite color fundus photograph reveals a solitary uveal metastatic cutaneous melanoma with an associated exudative retinal detachment. *Right:* A composite fluorescein angiograph of similar phase images demonstrates blockage of fluorescence and a lack of intrinsic vascularity.

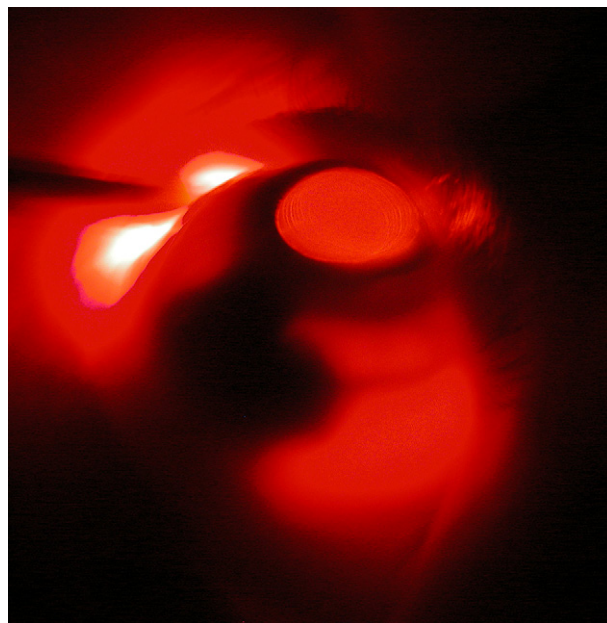


Fig. 3. Cutaneous melanoma metastatic to the eye and orbit. Transscleral transillumination of an eye containing a metastatic cutaneous melanoma reveals an irregularly shaped shadow extending to the ciliary body.

lipofuscin deposits.¹⁴ To complicate matters, even nonpigmented clumps of vitreous melanoma metastases have been reported.³⁵ In these cases, a prior history of malignant melanoma is exceedingly important for diagnosis.

Anterior chamber metastasis are believed to emanate from the adjacent iris root and head of the ciliary body.¹⁰ Conjunctival metastases have

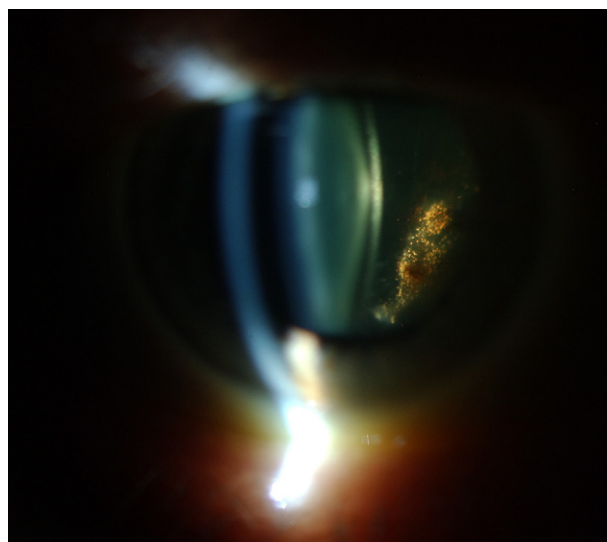


Fig. 4. Cutaneous melanoma metastatic to the eye and orbit. Slit lamp photography reveals clumps of melanoma cells in the posterior chamber.

been reported to be either melanotic or amelanotic and are most commonly located in the bulbar conjunctiva.^{39,41}

Differentiating among orbital tumors can also be challenging. Rare tumors such as primary orbital melanomas must also be considered; as should metastases from equally rare primary nonocular mucosal or pulmonary melanomas.

2. Pathology

It is difficult to differentiate between primary uveal melanoma and intraocular cutaneous melanoma by cytology or histopathology. However, in a patient suspected to have metastatic intraocular melanoma without detectable extraocular metastasis, histological findings can offer important corroborative evidence (making biopsy a crucial part of diagnosis).

With respect to cell-type, metastatic cutaneous melanomas rarely contain spindle cells and often contain epithelioid cells.²⁸ This is in clear distinction to primary iris melanomas (typically spindle cell type) and primary choroidal melanomas (commonly mixed cell, spindle-B, and epithelioid cell types).⁵⁵ Additionally, epithelioid malignant melanoma cells, regardless of origin, are cytologically identical.

Certain histopathologic findings in addition to epithelioid cell type favor a diagnosis of metastatic cutaneous melanoma. However, it is important to note the complexity and difficulty of differentiating primary uveal melanoma and metastatic malignant cutaneous melanoma on histology.²⁸ Multiple foci of tumor and tumor emboli within large (choroidal and retinal) blood vessels are more consistent with metastases.^{28,33} In addition, choroidal nevi are commonly found at the base of primary uveal melanomas; therefore, the absence of an underlying choroidal nevus is more consistent with the diagnosis of metastatic cutaneous melanoma.^{19,28,33} Although it has been reported, it is not generally accepted that histopathologic comparisons to the original cutaneous melanoma can help assure the diagnosis.⁷

Immunocytochemistry can help determine if the tumor expresses melanocyte markers (e.g., S100 protein) or markers of a more immature phenotype (e.g., HMB45).⁷ Currently, there are no immunohistochemical markers to distinguish a melanoma's cutaneous or choroidal origin. Potential future markers include antibodies directed against neuron specific enolase and alpha-melanocyte-stimulating hormone receptors.^{7,47}

In sum, although pathology cannot determine the origin of the melanoma, histopathology can support

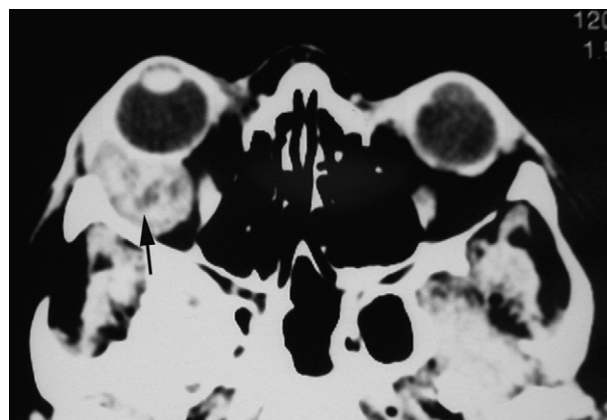


Fig. 5. Cutaneous melanoma metastatic to the eye and orbit. Computed radiographic tomography (CT) reveals a rounded intraconal metastatic cutaneous melanoma, surrounding the lateral rectus and inducing proptosis (arrow).

one's clinical impression. Therefore, fine-needle aspiration, vitrector-assisted biopsy, and, rarely, enucleation can provide enough cells or tissue to make the diagnosis of malignant melanoma and suggest its origin.^{21,24,25,34,40,49,61}

3. Radiographic Imaging

Ultrasound imaging is readily available in most eye centers and can assist with the evaluation of patients with intraocular and orbital metastases.⁴⁹ Ultrasound is commonly used to document, measure, and follow for evidence of tumor growth.⁵⁷ Orbital metastasis can be viewed and evaluated in association with adjacent extraocular muscles and optic nerve (Fig. 5). Extrascleral extension of primary choroidal melanoma extension can be diagnosed.⁵⁷ In practice, evaluations for internal tumor reflectivity and intrinsic vascular patterns can aid diagnosis and response to treatment.

Although computerized radiographic tomography (CT) is not typically helpful for most intraocular metastases (due to the small size of most lesions), it is particularly helpful for patients with orbital involvement due to its ability to visualize bony details.^{16,20} Thus, CT can be used to evaluate tumor-invasion of orbital bones, extension into the cranial cavity, and to reveal calcification.¹⁶ CT is an excellent screening tool to evaluate tumor involvement within the extraocular muscles (Fig. 5).

Magnetic resonance imaging (MRI) is superior to CT for visualization of soft tissue structures and can best establish the precise extent of the metastases within surrounding orbital structures.^{16,48} MRI can better reveal both intra-orbital, intracranial, and non-calcific optic nerve abnormalities.¹⁶

TABLE 1
Patient Characteristics by Ocular Site

	Site, No. (%) of Patients		
	Intraocular Only (n = 61)	Extraocular Only (n = 27)	Total (n = 93)
Male	34 (56)	16 (59)	54 (58)
Mean age at ocular presentation	50 years (range: 26–87)	55 years (range: 33–87)	51 years (range: 22–87)
Primary cutaneous site	n = 46	n = 16	n = 66
Trunk	21 (46)	3 (19)	26 (39)
Upper extremities	12 (26)	3 (19)	16 (24)
Lower extremities	6 (13)	7 (44)	14 (21)
Head and neck	7 (15)	3 (19)	10 (15)

Not all patients had information reported on each characteristic; due to these missing values, some totals do not add.

Positron emission tomography/computed tomography (PET/CT) is commonly and widely used to stage and guide therapy in patients with metastatic cutaneous and primary uveal melanoma.^{6,72} This combination of physiologic imaging (PET) and anatomic localization (CT) further offers whole body imaging to survey the entire patient for metastatic disease.^{23,43,59} Due to the incidence of concurrent pulmonary, intracranial, and bone metastasis seen in patients with ocular metastases, patients suspected to have metastatic cutaneous melanoma should be evaluated by total body PET/CT imaging and be co-managed by a medical oncologist.⁵⁹ Other forms of nuclear radiology have the potential to be useful, such as radionuclide labeling of monoclonal antibodies to melanoma antigens.⁵³

II. Patient Characteristics

A. DEMOGRAPHICS

A summary of patient characteristics is presented in Table 1. There were 93 patients included in 51 case reports. The vast majority of patients (82%) were between ages 30 and 70 at time of ocular diagnosis.

In dermatologic reviews, the average age of cutaneous melanoma diagnosis is 55 years.¹³ Interestingly, we found the age of primary cutaneous melanoma diagnosis in patients with eventual ocular metastases to be 48 years of age. It is important to note that they are generally younger than patients with primary choroidal melanoma (mean 60 years) both on initial diagnosis of the primary (48 years) and on ocular presentation (51 years).⁶⁷ However, the clinical relevance of these age differences is questionable given the broad age ranges.

In addition, patients with intraocular metastases tend to be younger than those with extraocular metastases by an average of about 5 years. Other studies have also noted that patients with intraocular

metastases are younger at presentation (median age: 46 years).⁵⁵ It appears that intraocular metastases occur in younger patients than do extraocular metastases, but it is also possible that patients with intraocular metastases simply present earlier. Although patients with intraocular metastasis are more likely to notice visual symptoms and seek earlier medical attention, it may not account for a 5-year difference.

B. CHARACTERISTICS OF THE PRIMARY TUMOR

The primary site of cutaneous melanoma metastatic to ocular structures was reported in 66 of the 93 patients (Table 1). The overall most common location was the trunk in 39% of patients, followed by the upper (24%) and lower (21%) extremities. Head and neck primary melanomas were the least common to metastasize to ocular structures accounting for only 15% of patients. These trends were also true for patients with only intraocular metastases as nearly half (21 of 46 patients, 46%) had primaries on the trunk. Although there were fewer patients (n = 16) with only extraocular metastases and known sites of primary cutaneous melanoma, they had more primaries on the lower extremities (7 patients, 44%) than other sites.

Likewise, the overall most common primary site of cutaneous melanomas is the trunk, accounting for up to 31% of tumors.⁷³ This is followed by head and neck in 22% of patients, upper extremity in 21%, and lower extremity in 20%.⁷³ Similar to our review, other reports in the literature have noted that up to 80% of ocular and orbital metastases arise from primaries on the trunk and upper extremities with very few primaries found on the head and neck.^{9,39} In general, cutaneous malignant melanomas of the middle and lower back, as well as mammary and supra-mammary areas, carry a worse prognoses, perhaps explaining their higher prevalence among tumors metastatic to the eye.³⁰

Although our literature review did not find sufficient data to report on the most common pathological subtype of melanoma metastatic to the eye and orbit, at least one autopsy study examined five patients with ocular metastases from cutaneous melanoma with known pathologic diagnosis.²⁶ All five patients had the superficial spreading variety of cutaneous melanoma, a subtype that accounts for 70% of total cutaneous melanomas but is rarely stage IV disease (1% of superficial spreading melanomas).^{13,26,72}

III. Metastatic Disease

A. OCULAR METASTASES

1. Sites of Ocular Metastases

Cutaneous melanoma metastasizes more commonly to intraocular versus extraocular structures (Table 2). In our structured review, 61 (66%) patients had only intraocular metastases, 27 (29%) patients had only extraocular metastases, and 5 (5%) patients had both intraocular and extraocular metastases.

a. Intraocular Metastases

The uvea has been found to harbor up to 75% of intraocular cutaneous melanoma metastases with choroidal involvement occurring in 40–46% of these eyes.^{35,37,55,68} This is most likely due to the choroid receiving 84% of the blood flow supplying the eye.⁵ Previous studies have shown retinal involvement in 27% of intraocular metastases, vitreous involvement in 18%, and vitreo-retinal in up to 49%.^{35,55,68} In contrast to these reports, we found the vitreous (17 patients, 28%) was more involved in intraocular metastases than was the retina (11 patients, 18%). In addition, 7 of the 11 patients with retinal involvement also had vitreous involvement, and there were 8 patients with exclusively vitreous metastases. Other ocular sites of cutaneous metastatic melanoma have previously been reported as follows: iris (23%), ciliary body (22%), iris-ciliary body (35%), optic disk (12%), and anterior chamber (11–13%).^{35,55,68}

b. Extraocular Metastases

Over one third of patients (32 of 93 patients, 34%) had metastases to the orbit, extraocular muscles, or eyelid. Extraocular muscle involvement is particularly prevalent in cutaneous melanoma, and was specifically reported in eight of 29 patients (28%) with orbital metastases (Fig. 5). Several studies have noted

TABLE 2

Site of Ocular Metastases

	Site, No. (%) of Patients	
	Total (n = 93)	Intraocular Only (n = 61)
Extraocular	32 (34)	–
Orbit, including extraocular muscles ^a	29 (31)	–
Eyelid ^b	5 (5)	–
Uveal	39 (42)	36 (59)
Choroid ^c	25 (27)	24 (39)
Iris ^d	11 (12)	9 (15)
Ciliary body ^e	8 (9)	8 (13)
Vitreo-retinal	22 (24)	22 (52)
Vitreous ^f	17 (18)	17 (28)
Retina ^g	11 (12)	11 (18)
Optic disc, nerve ^h	4 (4)	4 (7)
Anterior segment	18 (19)	15 (25)
Conjunctiva ⁱ	13 (14)	10 (16)
Anterior chamber ^j	6 (6)	5 (8)

Several patients had more than one site of ocular involvement, therefore some totals are >100%. References reviewed for data collection:

^aOrbit: 4,9,11,16,19,31,48,51–53,58,71,75,77,80

^bEyelid: 19,36,39,80

^cChoroid: 3,7,10,17–20,33,46,50,62,63,76,80

^dIris: 17,37,41,51,75,76,80

^eCiliary body: 1,10,17,37,41,55,78,80

^fVitreous: 8,10,14,15,20,35,38,54,56,60,68,70,74,80

^gRetina: 5,8,17,20,46,56,68–70,80

^hOptic disc, nerve: 8,20,54,78

ⁱConjunctiva: 18,22,39,41,44,66,79,80

^jAnterior chamber: 10,14,20,39,51,55,78

the predilection for extraocular muscles from metastatic cutaneous melanoma.^{16,32,52,80}

c. Synchronous Intraocular and Extraocular Metastases

Only 5 of 93 patients developed synchronous intraocular and extraocular metastases. One patient had extraocular involvement exclusively in one eye and intraocular involvement exclusively in the other eye.¹⁹ The other four patients had concurrent intra- and extraocular metastases in a single eye.^{39,75,80} The patients with both intraocular and extraocular metastases also tended to be younger, with four of five more than a decade under the average age of 51 years (22, 36, 37, 38 years). The conjunctiva was involved in three patients with two of these also involving the eyelid.^{39,80} Uveal tract involvement was present in three patients (all having orbital or extraocular muscle metastases).^{19,75,80}

All five patients with intraocular and extraocular metastases from cutaneous melanoma had concurrent nonocular metastases at the time of ocular diagnosis. Lymph node involvement was present in all four patients that reported metastatic site and

TABLE 3
Presenting Signs and Symptoms

	Site, No. (%) of Patients		
	Intraocular Only (n = 58)	Extraocular Only (n = 26)	Total (n = 89)
Decreased vision	36 (62)	7 (27)	46 (52)
Painful eye	10 (17)	8 (31)	19 (21)
Tumor noticed by patient or on exam	8 (14)	7 (27)	17 (19)
Proptosis	0	15 (58)	16 (18)
Diplopia	0	14 (54)	14 (16)
Floater	13 (22)	0	14 (16)
Redness/red eye	9 (16)	3 (12)	12 (13)
Other visual abnormalities	3 (5)	0	3 (3)
Other signs/symptoms	9 (16)	10 (38)	19 (21)

Many patients had multiple signs/symptoms; therefore some totals are >100%.

three of these four patients also had cutaneous metastases. Two patients had widespread metastases. Survival time varied from less than 3 to 30 months, and one patient was alive on follow up of less than 5 months.^{19,39,75,80}

2. Laterality

In 78 patients with laterality reported, left- and right-sided metastases were equally divided (left: 32 patients, 41%; right: 31 patients, 40%). Fifteen (19%) patients presented with bilateral metastases. The remaining 15 patients were noted to have unilateral involvement, although no specific side was reported.^{63,74,80}

Overall, there have been 108 eyes in 93 patients reported with metastases from cutaneous melanomas. As would be expected given the overall higher proportion of intraocular metastases (66% of all patients), three-fourths of left-sided unilateral metastases were intraocular (24 of 32 patients, 75%). However, only slightly over half (17 of 31 patients, 55%) of right-sided metastases were intraocular. Two-thirds (10 of 15 patients, 67%) of bilateral metastases were exclusively intraocular.

3. Symptoms at Presentation

Presenting signs and symptoms are reported in Table 3 and were reported in almost all cases (89 of 93 patients, 96%). Most patients presented with decreased vision (46 patients, 52%) or eye pain (19 patients, 21%). Seventeen (19%) patients had ocular metastases discovered because a tumor was visible either by the patient or noticed on physical examination (Fig. 6).

a. Intraocular Metastases

Visual abnormalities occurred predominantly in patients with intraocular involvement. Moreover,

among patients with exclusively intraocular metastases, these were the most common symptoms. Thirty-six of the 46 (78%) patients with decreased vision had exclusively intraocular metastases. Also, 13 of 14 (93%) patients with floaters had only intraocular metastases. The remaining tumor-related visual abnormalities included scotoma, photopsia, and metamorphopsia.^{3,80}

In general, choroidal metastases (any primary) can cause a red eye, decreased or blurred vision, visual field defects, floaters, and pain.^{17,29} Cutaneous melanoma metastases to the vitreous commonly present with floaters or decreased vision.^{15,20,35} These were common complaints among the patients reviewed and not surprising given the prevalence of choroidal and vitreous metastases.

Conjunctival tumors from malignant melanoma tend to be visible, bulbar, and pigmented masses.^{39,41,42,64} Of the 13 reported cutaneous melanoma metastases to the conjunctiva, 8 had lesions noticed by the patient or on clinical examination.

b. Extraocular Metastases

Of those patients with exclusively extraocular metastases, proptosis (15 patients, 58%) and diplopia (14 patients, 54%) were the most common presenting symptoms. Fewer patients presented with visual abnormalities (decreased vision, metamorphopsia or floaters). Orbital cutaneous melanoma metastases most often presented with diplopia and motility disorders due to extraocular muscle involvement (Fig. 7).^{16,31,52,80} Lastly, metastatic cutaneous melanoma to the orbit may be well-circumscribed and mimic a benign tumor (Fig. 5).⁶⁵

4. Secondary Ocular Diseases

Secondary ocular complications due to cutaneous melanoma metastases were reported in 55 patients.



Fig. 6. Cutaneous melanoma metastatic to the eye and orbit. External photographs demonstrate two pigmented lesions on the right arm and a nodular cutaneous metastatic tumor in the left lower eyelid (arrows) in a patient with uveal metastatic melanoma of cutaneous origin.

Forty-eight of these patients had exclusively intraocular metastases. Over half (30 patients, 54%) developed glaucoma and over one-fourth (15 patients, 27%) specifically developed neovascular glaucoma. Iris neovascularization may be present at diagnosis or develop as the tumor progresses.¹⁵ All cases of increased intraocular pressure occurred in patients with some intraocular involvement.

Factors contributing to increased intraocular pressure include tumor consuming the outflow system or cellular debris (tumor or inflammatory) obstructing the trabecular meshwork.¹⁷ Patients with metastases characterized by cellular tumor material deposits on the iris, lens surface, and trabecular meshwork are particularly at risk.¹⁰ In addition, patients with secondary iritis, iris bombe, and anterior synechiae were noted to have increased

intraocular pressure.¹ Lastly, a large choroidal tumor can induce angle closure due to choroidal detachment.¹⁷

Other less frequent secondary complications included uveitis or iridocyclitis seen in 10 (18%) patients and vitreous detachment, traction, or hemorrhage in 7 (13%) patients. Also reported were retinal detachments in seven (13%) patients and subretinal fluid, hemorrhage, or infiltrates in three (5%) patients. Bullous keratopathy has been reported to develop from massive anterior chamber involvement.¹⁵ Therapy that led to tumor necrosis has also induced black hypopyon.^{1,78}

Only three patients with extraocular involvement were reported to develop dilated retinal vessels, central retinal artery occlusion, or a distorted eyelid margin.^{36,51,52}

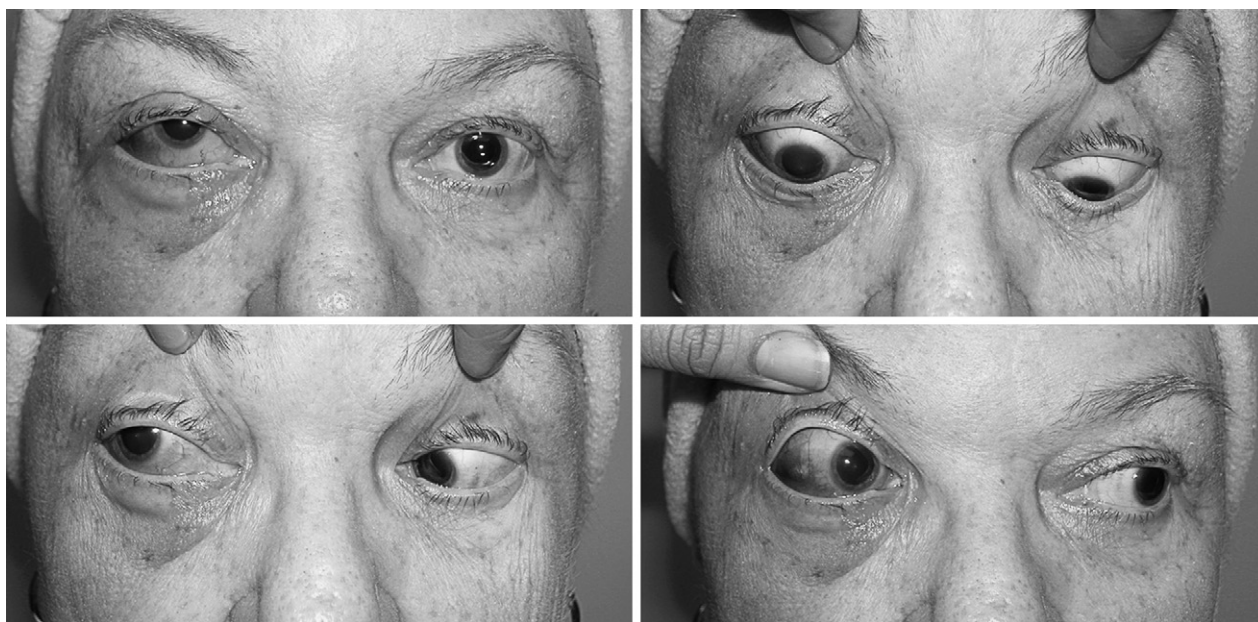


Fig. 7. Cutaneous melanoma metastatic to the eye and orbit. External photographs of a patient with orbital metastatic cutaneous melanoma reveals a right hypertropia and restriction in all fields of gaze.

TABLE 4
Sites of Non-ocular Metastases

	Site, No. (%) of Patients		
	Intraocular Only (n = 52)	Extraocular Only (n = 16)	Total (n = 73)
Cutaneous, subcutaneous	21 (40)	9 (56)	33 (45)
Widespread*	18 (34)	9 (56)	29 (40)
Lymph nodes	17 (32)	7 (44)	28 (38)
Central nervous system	20 (38)	5 (31)	25 (34)
Lungs	16 (30)	4 (25)	20 (27)
Liver	12 (23)	5 (31)	18 (25)
Other abdominal organs	4 (8)	3 (19)	7 (10)
Other**	6 (11)	0	6 (8)
Local recurrence	5 (9)	0	5 (7)
Bone, bone marrow	0	3 (19)	4 (5)
None	5 (9)	0	5 (7)

Many patients had multiple sites of non-ocular metastases; therefore some totals are >100%.

*"Widespread" included reported "widespread metastases" or documented metastases to three organs in addition to ocular structures.

**Other sites included kidneys, ovaries, heart, neck, mediastinum, mucosa, sinuses, adrenal glands, and vocal cords.

5. Timing

Timing between the primary cutaneous melanoma and discovery of ocular metastases was reported in 90 of 93 patients. Eighty-eight of these 90 (98%) patients had a history of cutaneous melanoma at the time of ocular presentation, and the remaining two (2%) had primaries diagnosed subsequent to ocular presentation. The mean interval of patients with metastases discovered after known primary cutaneous melanoma was approximately 3 years (40 months) with a median of 36 months (range: 0 to 120 months). The adjusted mean time interval was calculated after excluding four patients with intervals more than 2 standard deviations above the overall mean (46 ± 44 months, range: 0–240 months, outliers: 144, 180, 192, 240 months). Almost three-fourths (65 patients, 72%) had ocular metastases within 5 years of diagnosis of primary cutaneous melanoma. A surprisingly large number (14 patients, 16%) went over 7 years from primary disease to ocular metastasis.

The timing of intraocular (n = 56, mean = 42 months, median = 36) and extraocular (n = 24, mean = 39 months, median = 32) disease was similar. In contrast, other studies have reported shorter intervals for intraocular metastases and longer intervals for extraocular metastases. Other reports have found that intraocular involvement occurred at a mean of 22–26 months, ranging from 0 to 56 months.^{55,80} Orbital tumors have been reported at a mean of 66 months (range: 21–106 months).⁸⁰

6. Incidence of Concurrent Metastases at Ocular Diagnosis

At the time of ocular presentation, most reported patients with cutaneous melanoma either had pre-

viously diagnosed widespread systemic metastases or disseminated disease is discovered on metastatic work-up (Fig. 6).^{17,19,33} In one report, all 10 patients with intraocular metastases from primary cutaneous melanoma were found to have concurrent disseminated metastases at diagnosis.¹⁷

In our review, the timing of non-ocular metastases in relation to ocular metastases was reported in 76 patients. We found that 68 of these 76 (89%) patients had at least one other non-ocular distant metastasis at ocular presentation. There was no difference between patients with intraocular versus extraocular disease. The remaining eight (11%) patients with negative metastatic evaluations were all later diagnosed with non-ocular systemic metastases. Though few patients present with ocular metastases as the first sign of cutaneous melanoma spread, nearly all go on to manifest widespread metastases.^{3,15,68} We found only five patients with exclusively intraocular metastases in whom additional metastatic sites were never reported.

B. LOCATIONS OF NON-OCULAR METASTASES

The location of non-ocular metastases was reported in 73 of 93 patients (Table 4). The most frequent sites were cutaneous and/or subcutaneous metastases in 33 (45%) patients and lymph node metastases in 28 (38%) patients. The next three most common sites of metastases were the central nervous system (25 patients, 34%), lungs (20 patients, 27%), and liver (18 patients, 25%).

Dermatologic reviews report the most common sites of metastases in cutaneous melanoma are lungs (18–36%), liver (14–29%), brain (12–20%), and bone (11–17%).²⁷ However, 42–57% have already spread to distant lymph nodes, other cutaneous

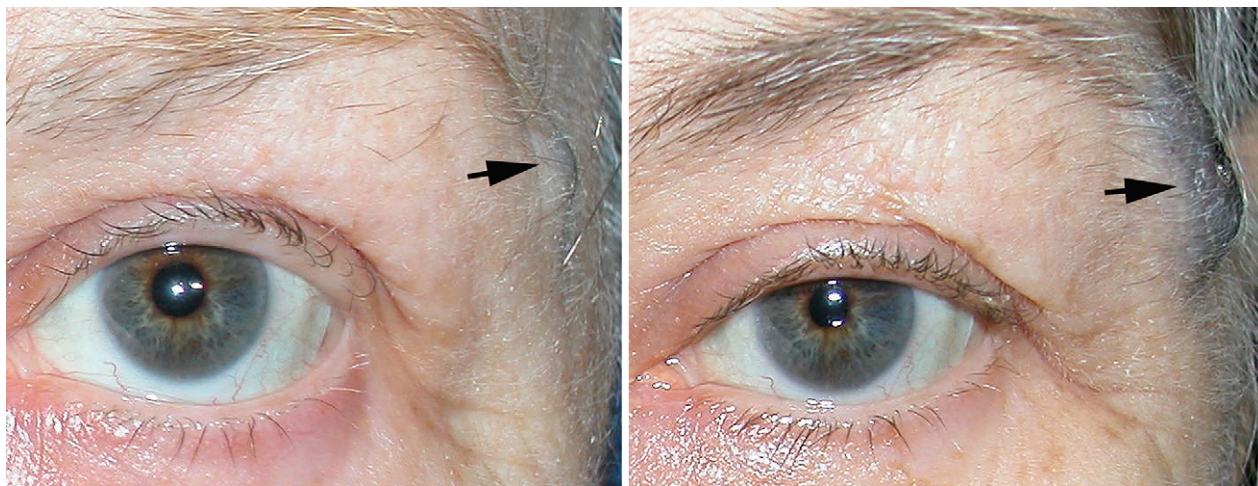


Fig. 8. Cutaneous melanoma metastatic to the eye and orbit. External photographs reveal a cutaneous metastatic cutaneous melanoma of the brow that more than quadrupled in size within 1 month and was associated with disseminated metastatic melanoma (arrows).

sites, and subcutaneous tissues by the time of other metastases (Figs. 6 and 8).²⁷ Patients with malignant cutaneous melanoma and ocular metastases appear to have more frequent central nervous systems metastases and less frequent bone metastases compared to the overall pattern of cutaneous melanoma spread. For example, almost half of patients with vitreous metastases also have cerebral metastases eventually diagnosed.³⁸ Other studies of intraocular metastases suggest lung metastases most often accompanied ocular metastases (50%) followed by subcutaneous nodules (40%), liver (30%), and brain, lymphatics, and ovaries in 10% each.¹⁷ Therefore, we suggest a complete metastatic survey for patients suspected of having cutaneous melanoma metastatic to the eye or orbit.

It is interesting to note that 20 (80%) of the 25 patients with central nervous system metastases had exclusively intraocular involvement. Arterial spread (via the internal carotid artery) has been theorized to explain the predominance of intraocular metastases in patients with intracranial disease.^{37,51} In addition, 16 (80%) of the 20 patients with lung metastases had solely intraocular disease. All four patients with bone and/or bone marrow metastases had some extraocular metastatic disease with three (75%) of four having exclusively extraocular metastases.

Twenty-nine (40%) patients had “widespread” metastases. We defined “widespread” as either reported as such or documented metastases to at least three other organs in addition to the eye, adnexae, or orbit. Almost one-third of patients (18 of 53 patients, 34%) with only intraocular disease and more than half of patients (9 of 16 patients, 56%) with only extraocular metastases had such

widespread metastases. Nearly all of these patients (24 of 29 patients, 83%) had concurrent non-ocular metastasis at ocular diagnosis. It is not surprising for patients to have widespread disease by the time ocular or orbital metastases from cutaneous melanoma is diagnosed.^{17,52} Fishman, et al discussed autopsy findings on 15 consecutive patients with malignant cutaneous melanoma and found five patients with asymptomatic intraocular metastases.²⁶ All had associated lung, liver, and central nervous system metastases.²⁶

IV. Treatment

A. OCULAR-SPECIFIC TREATMENT

Ocular-specific treatments were reported in 80 of 93 patients (Fig. 9). Thirty-four (43%) patients received radiotherapy to the eye and 22 (28%) patients had excisions or resections of the ocular tumors. Sixteen (20%) patients had enucleation, evisceration, or exenteration. There were 14 (18%) patients who received observation as treatment and one case of spontaneous remission.⁶²

In patients with exclusively intraocular tumors, the most common treatment modality was radiotherapy in 22 (39%) of 57 patients. Fourteen (25%) patients with only intraocular metastases had enucleation or evisceration. Eight additional treatments for intraocular metastases included vitrectomy (4), subconjunctival chemotherapy (2), direct confluent laser photocoagulation (1), and cryotherapy (2).^{22,38,39,56,60,68,70}

Of the patients with exclusively extraocular metastases, the most common treatment was excision or resection of a tumor mass from 11 of 19

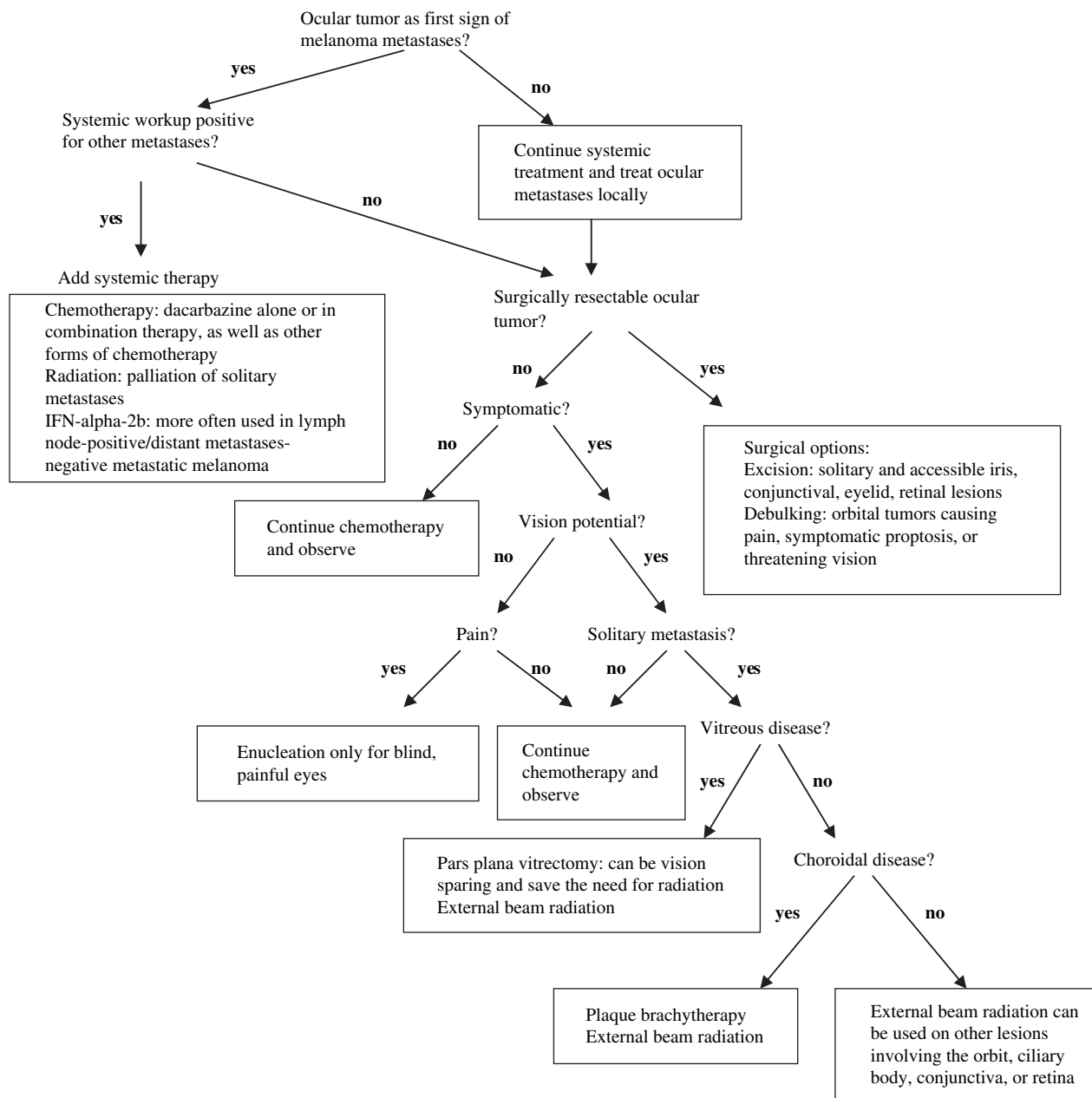


Fig. 9. Analysis of tumor treatment options based on this review of the literature and our clinical experience.

(58%) patients. Radiation therapy was used in nine (47%) of these patients. Only one patient with exclusively extraocular involvement was treated by orbital exenteration, and one patient with both intraocular and extraocular metastases underwent enucleation as treatment.^{19,48}

In our center, a combination of surgical resection with adjuvant external beam radiation therapy is typically employed. The goal of surgery is to decrease tumor volume, and radiation addresses presumed residual microscopic disease. However, primary radiation therapy can be employed when surgery is not possible.

B. SYSTEMIC TREATMENT

Sixty-three patients were reported to receive systemic, non-ocular treatments (not including excision of the primary cutaneous melanoma). Most (44 patients, 70%) received systemic chemotherapy. This is not surprising in that treatment of metastatic melanoma generally involves a chemotherapeutic regimen including dacarbazine (DTIC) either alone or in a combination therapy.⁷²

Whereas 60% (27 of 45 patients) of patients with only intraocular involvement received chemotherapy, 93% (13 of 14 patients) with extraocular involvement received chemotherapy.

TABLE 5
Ocular Outcomes in Patients with Unilateral Involvement

	Site, No. (%) of Patients		
	Intraocular Only (n = 40)	Extraocular Only (n = 8)	Total (n = 50)
Complete control or resolution	13 (33)	3 (38)	17 (34)
Incomplete tumor regression	9 (23)	2 (25)	11 (22)
No change	1 (3)	0	1 (2)
Tumor progression without enucleation	4 (10)	2 (25)	7 (14)
Eventual loss of eye	13 (33)	1 (13)	14 (28)

Not all patients with unilateral disease had reported outcomes; therefore, some values are missing.

Radiation therapy targeting sites other than the eye was performed in 16 (25%) patients. Smaller numbers of patients received immunotherapy (10 patients, 16%) and BCG-vaccination (8 patients, 13%).

C. CURRENT AND FUTURE TREATMENTS

A preferred therapy for ocular metastases has not been clearly elucidated as many approaches from systemic treatment to local therapy have been tried with mixed results.⁸⁰ Patients with ocular involvement generally have or will have widespread melanoma metastases; therefore, chemotherapy is often a part of treatment.^{3,17,52,72} Depending on the expected outcome of the patient and the goals of therapy, regimens have included chemotherapy, radiation, or surgery, although all these methods are used for palliation.^{7,17,19,80} It is important to control symptoms, improve vision, and enhance ocular function in patients with widespread metastases.¹⁶

Patients with asymptomatic intraocular metastases who are already receiving chemotherapy have been managed with observation.⁶⁸ Also patients with severe, advanced disease can be observed.⁵⁰ Zografos et al found limited data on the ability of systemic chemotherapy and immunotherapy to control intraocular tumors; therefore, these treatments were not recommended.⁸⁰ Others have suggested that biologic response modifiers with chemotherapy can produce a better response rate.⁷²

For patients with isolated ocular metastases, radiation therapy can help reduce tumor burden.⁵⁰ There have been several reports of regression of choroidal metastases with plaque radiotherapy.^{3,63} Solitary orbital metastases can also be treated with exenteration and radiation, with or without chemotherapy.¹⁶ However, enucleation or exenteration do not typically prolong survival; therefore, most recommend that only blind, painful eyes should be enucleated.^{50,52,68}

There exist more current approaches including antimetabolites, and biotherapies used alone and in

combination. However, a complete review of current approaches to the treatment of metastatic melanoma is complicated and beyond the scope of this review.

V. Outcomes

A. OCULAR OUTCOMES

1. Unilateral Ocular Metastases

Of the patients with unilateral involvement, 50 had reported outcomes (Table 5). Most patients (28 patients, 56%) had some improvement of ocular disease with treatment. However, over one-fourth of patients (14 patients, 28%) required eventual enucleation, evisceration, or exenteration. Seven (14%) patients had progression that did not result in enucleation. Although reported response to treatment was similar, many more enucleations (13 versus 1) were required for patients with intraocular versus extraocular disease.

A comparison of patients receiving chemotherapy, ocular radiation, or chemotherapy and radiation is presented in Table 6. Although the total number of patients is small, it appeared that patients receiving any ocular radiation had the best results with 14 (70%) of 20 patients having at least some tumor resolution. Ten (48%) of 21 patients receiving any chemotherapy had at least some resolution. Interestingly, only seven patients received synchronous chemotherapy and radiation with none achieving local tumor control. Although there is some promise of relief in patients with ocular melanoma metastases; treatment has been inconsistently beneficial.⁵⁰

2. Bilateral Ocular Metastases

In our systematic review, 15 patients had bilateral ocular involvement, and 11 eyes have outcome data. Of these eyes, only one had complete tumor control and three displayed partial tumor regression.^{19,35,78}

TABLE 6
Ocular Outcomes for Specific Treatments in Patients with Unilateral disease

	Treatment modality, No. (%) of patients		
	Chemo (n = 21)	Ocular radiation (n = 20)	Both (n = 7)
Complete control or resolution	4 (19)	6 (30)	0
Incomplete tumor regression	6 (29)	8 (40)	4 (57)
No change	0	1 (5)	0
Tumor progression without enucleation	6 (29)	2 (10)	1 (14)
Eventual loss of eye	5 (24)	3 (15)	2 (29)

Total receiving any chemotherapy: n = 32 patients with unilateral involvement. There are 21 patients with known ocular outcomes of that 32. Chemotherapy plus ocular radiation: 12 patients with unilateral metastases had both chemotherapy and ocular radiation. Only 7 of those 12 have known ocular outcomes. Total receiving radiation to the eye: n = 28 with unilateral metastases and 20 also have known ocular outcomes.

Four eyes had tumor progression without enucleation, two eyes were enucleated, and one was unchanged.^{19,20,35,46,56,68}

These findings can be used as a general guide when planning and discussing palliative treatment with affected patients (Fig. 9).

B. PATIENT SURVIVAL

Patient outcomes are presented in Fig. 10. Seven patients were alive on last follow-up. Thus, the interval between ocular metastases and death was reported in 67 patients. The mean survival time was 7.3 months, with 53 of 68 (78%) patients deceased within 12 months of their ocular presentation.

Patients with only extraocular metastases (n = 23 patients) survived an average of 7.5 months whereas those with only intraocular metastases (n = 41 patients) survived 6.6 months. The five patients with both intraocular and extraocular metastases had variable survivals of <3 months, 5 months, 14 months, and 30 months. The fifth was alive at the time of publication.

On last follow-up, seven patients were still alive and their follow-up times were variable (2, 3, 12, 24, 24, 30, and 72 months). Two additional patients were alive without a reported follow-up time. There were eighteen patients without reported outcome data or that died of non-cancer related causes (e.g., suicide, myocardial infarction).^{69,78}

In contrast to previously published reviews, our comprehensive review found shorter survival durations with total survival averaging 7.3 months, patients with intraocular metastases averaging 6.6 months and extraocular averaging 7.5 months. Zografos et al found that patients with orbital metastases had better survival (19.7 months) than those with intraocular metastases (8.8 months).⁸⁰ Gunduz et al found a mean survival of 14 months in a series of patients with cutaneous melanoma metastatic to the vitreous cavity.³⁵ However, over 90% of patients with any ocular metastases from cutaneous melanoma do not survive past 12 months.^{14,80}

VI. Conclusions

In the United States, the incidence of melanoma is increasing faster than any other cancer, doubling every 10 years.^{22,45,72} Recent reviews have estimated that one in 82 women and one in 58 men will develop cutaneous melanoma during their lifetimes.⁷² This accounts for more than 55,000 new cases per year and 7600 deaths.⁷²

Unfortunately, survival in patients with metastatic cutaneous melanoma is poor, averaging less than 9 months.⁷² These patients generally receive palliative

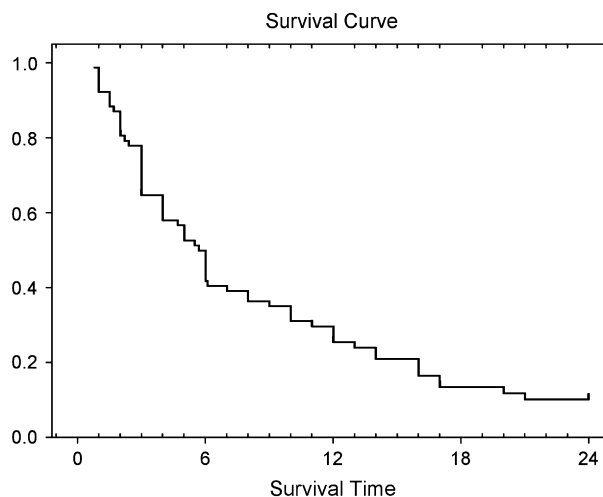


Fig. 10. Cutaneous melanoma metastatic to the eye and orbit. Kaplan-Meier survival curve of 72 patients with known time from ocular presentation to death. Only deaths due to metastatic melanoma were used as end points with 2 years as “end of study.” Censored patients were those alive at follow-up less than 24 months, deaths due to other causes, and outcomes past 24 months (death or alive).

therapy for metastatic disease. Therefore, we have presented this review to improve our knowledge of the presentation and clinical features associated with metastatic cutaneous melanoma to the eye, adnexae, and orbit. Clearly, prompt diagnosis and treatment of the ocular disease offers the best chance to preserve and improve each patient's quality of life. Therefore, we recommend periodic ophthalmic examinations of all patients diagnosed with metastatic cutaneous melanoma.

VII. Methods of Literature Search

The references in our review were obtained using the following databases: National Library of Medicine's Pubmed, Medline, and EMBASE, excluding any non-English language articles. References within these articles were also reviewed. The keywords used were *cutaneous melanoma*, *malignant cutaneous melanoma*, *metastatic*, *metastases*, *metastasis*, *eye*, *ocular*, *orbit*, *choroid*, *conjunctiva*, *iris*, *retina*, *intraocular*, *extraocular*, *extraocular muscles*, *eyelid*. Cases reported from 1975 to 2007 were included because dacarbazine was initially used in metastatic melanoma in 1975, and it remains a mainstay of metastatic melanoma treatment today. Only case reports, case series, or reviews of cutaneous melanoma with metastases to ocular structures were included in data collection. Excluded were primary choroidal melanomas, primary eyelid melanomas, and pulmonary or non-cutaneous melanomas metastasizing to the eye.

Cases reporting most of the following information were included in data collection: sex, age at ophthalmic diagnosis of metastases, primary cutaneous site, time interval between primary cutaneous melanoma and ocular metastases, site(s) of ocular metastases, laterality of ocular metastases, symptoms of ocular metastases, site(s) of non-ocular metastases, systemic treatment in addition to local excision of primary melanoma, specific ocular treatment, ocular outcomes, and time between ocular diagnosis and death. Fifty-one such reports of 108 eyes in 93 patients were found.

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The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

This work was supported by The EyeCare Foundation, Inc., New York, New York. <http://eyecarefoundation.org>

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